increased by opportunistic infections, and that the chronic loss of Trp initiates mechanisms responsible for cachexia, dementia and diarrhoea and possibly immunosuppression of AIDS patients (Brown, et al., 1991, Adv. Exp. Med. Biol., 294: 425-35).

[0011] Further evidence for a tumoural immune resistance mechanism based on tryptophan depletion comes from the observation that most human tumours constitutively express IDO, and that expression of IDO by immunogenic mouse tumour cells prevents their rejection by preimmunized mice. This effect is accompanied by a lack of accumulation of specific T cells at the tumour site and can be partly reverted by systemic treatment of mice with an inhibitor of IDO, in the absence of noticeable toxicity. It has also been shown that the IDO inhibitor, 1-methyl-tryptophan (1-MT), can synergize with chemotherapeutic agents to reduce tumour growth in mice, (Muller et al., 2005, Nature Med., 11: 312-9), suggesting that a reduction in Trp catabolism may also enhance the anti-tumour activity of other cancer therapies.

[0012] IDO degrades the indole moiety of tryptophan, serotonin and melatonin, and initiates the production of neuroactive and immunoregulatory metabolites, collectively known as kynurenines. Tryptophan metabolism and kynurenine production might represent a crucial interface between the immune and nervous systems (Grohmann, et al., 2003, Trends Immunol., 24: 242-8). In states of persistent immune activation, availability of free serum Trp is diminished and, as a consequence of reduced serotonin production, serotonergic functions may also be affected (Wirleitner, et al., 2003, Curr. Med. Chem., 10: 1581-91). Tryptophan depletion has been associated with mood and psychiatric disorders such as schizophrenia, depression, panic disorder, seasonal affective disorder.

[0013] Tryptophan metabolites such as kynurenine, produced by IDO1, inhibit immunosurveillance in cancer by arresting T cells in the G1 phase of the cell cycle, promoting T-cell and dendritic cell apoptosis, and supporting regulatory T-cell generation. In addition, tryptophan metabolites have been found to negatively affect natural killer cell function.

[0014] Activation of the kynurenine pathways and production of neuroactive metabolites of tryptophan has been shown to be involved in Huntingdon's disease, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis, AIDS dementia complex, stroke and epilepsy.

[0015] Tryptophan is the precursor of serotonin (5-HT), thus increased tryptophan catabolism may play a role in the neuropsychiatric side effects caused by reducing central 5-HT synthesis, such as depressive symptoms and changes in cognitive function. Furthermore, kynurenine metabolites such as 3-hydroxy-kynurenine (3-OH-KYN) and quinolinic acid (QUIN) have toxic effects on brain function. 3-OH-KYN is able to produce oxidative stress by increasing the production of reactive oxygen species (ROS), and QUIN may produce overstimulation of hippocampal N-methyl-D-aspartate (NMDA) receptors, which leads to apoptosis and hippocampal atrophy. Both ROS overproduction and hippocampal atrophy caused by NMDA overstimulation have been associated with depression (Wichers and Maes, 2004, J. Psychiatry Neurosci., 29: 11-17). Thus, increased tryptophan catabolism activity may play a role in depression.

[0016] To date, the majority of research has focussed on direct inhibition of IDO as a means to reducing tryptophan catabolism, increasing Trp and decreasing kynurenine. For example, oxadiazole and other heterocyclic IDO inhibitors are reported in US 2006/0258719 and US 2007/0185165. Methods of measuring tryptophan levels and tryptophan degradation are routine in the art (Huang et al, 2013).

[0017] Further research has focussed on direct inhibition of TDO as a means of reducing Trp catabolism, such as reported in PCT/EP2014/076311.

[0018] Considering the experimental data indicating a role for Trp catabolism in immunosuppression, tumour resistance and/or rejection, chronic infections, HIV-infection, AIDS, autoimmune diseases or disorders, and immunologic tolerance and prevention of foetal rejection in utero, therapeutic agents aimed at suppression of tryptophan degradation are desirable. Suppression of tryptophan catabolism can be used to activate T cells and therefore enhance T cell activation when the T cells are suppressed by pregnancy, malignancy or a virus such as HIV. Suppression of tryptophan catabolism may also be an important treatment strategy for patients with neurological or neuropsychiatric diseases or disorders such as depression.

[0019] It has now been identified that some IDO inhibitors increase expression of IDO protein and such increased expression can continue for periods of time after the removal of the compound. Such activity would be considered unfavourable by a person skilled in the art as elevated expression would classically result in a greater level of Trp catabolism. A more favourable solution would be to identify compounds that have the ability to reduce the expression of IDO. More preferably a favourable solution would be to identify compounds that are able to reduce expression of IDO for durations after removal of the compound.

[0020] It has now been identified that the compounds of the invention are capable of reducing tryptophan catabolism, increasing Trp and decreasing kynurenine. More particularly, it has been identified that a compound of the invention is useful in the treatment of conditions associated with the abnormal or elevated catabolism of tryptophan.

[0021] Checkpoint Inhibitor—Combinations Background Under normal physiological conditions, immune checkpoints are crucial for the maintenance of self-tolerance (i.e. prevention of autoimmunity) and also to protect tissues from damage when the immune system is responding to pathogenic infection.

[0022] The expression of immune-checkpoint proteins can be dysregulated by tumours as another important immune resistance mechanism.

[0023] Direct T-cell recognition of tumour cells requires the presentation of antigenic peptides by MHC (major histocompatibility complex) molecules. These peptides are generated by proteasomal digestion and transported to the endoplasmic reticulum, where they are first loaded onto nascent MIIC molecules, which ultimately transport them to the cell membrane.

[0024] CD28 is the master costimulatory receptor expressed on T cells and enhances T-cell activation upon antigen recognition when the antigen presenting cell (APC) expresses its ligands, B7-1 and B7-2. Tumour antigen must be processed and presented by the MIIC complex to activate T cells. CTLA-4 is rapidly expressed on T cells once antigen is recognized, and it binds the same ligands (B7.1/2) as CD28 but at higher affinity, thereby counterbalancing the costimulatory effects of CD28 on T-cell activation. Tumour-specific T-cell activation leads to proliferations and effector